



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁴ : G01N 31/00		A1	(11) International Publication Number: WO 87/06343 (43) International Publication Date: 22 October 1987 (22.10.87)
<p>(21) International Application Number: PCT/US87/00796</p> <p>(22) International Filing Date: 6 April 1987 (06.04.87)</p> <p>(31) Priority Application Number: 849,758</p> <p>(32) Priority Date: 9 April 1986 (09.04.86)</p> <p>(33) Priority Country: US</p> <p>(71) Applicant: BIONOSTICS, INC. [US/US]; Eight Craig Road, Acton, MA 01720 (US).</p> <p>(72) Inventor: CHIANG, Ching ; Eight Fernwood Road, Acton, MA 01720 (US).</p> <p>(74) Agents: BROOK, David, E. et al.; Hamilton, Brook, Smith & Reynolds, Two Militia Drive, Lexington, MA 02173 (US).</p>		<p>(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: MULTIPLE CONTROL STANDARD FOR BLOOD ANALYSIS</p> <p>(57) Abstract</p> <p>A multiple control standard for the use in the quality assurance of blood analysis instrumentation systems. The liquid control standard is able to act as a control standard for blood gas instrumentation systems measuring pH, pCO₂ and pO₂ of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and as a liquid control standard for ion selective electrode instrumentation systems for the measuring of electrolytes such as Na and K ions in the blood.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austria	FR France	ML Mali
AU Australia	GA Gabon	MR Mauritania
BB Barbados	GB United Kingdom	MW Malawi
BE Belgium	HU Hungary	NL Netherlands
BG Bulgaria	IT Italy	NO Norway
BJ Benin	JP Japan	RO Romania
BR Brazil	KP Democratic People's Republic of Korea	SD Sudan
CF Central African Republic	KR Republic of Korea	SE Sweden
CG Congo	LI Liechtenstein	SN Senegal
CH Switzerland	LK Sri Lanka	SU Soviet Union
CM Cameroon	LU Luxembourg	TD Chad
DE Germany, Federal Republic of	MC Monaco	TG Togo
DK Denmark	MG Madagascar	US United States of America
FI Finland		

MULTIPLE CONTROL STANDARD FOR BLOOD ANALYSISBackground of the Invention

Clinical laboratories employ a variety of instrumentation systems for the analysis of patient samples. Frequently, three types of instruments are used to analyze particularly significant properties of fresh blood for diagnosis of respiratory-pulmonary ailments. These instruments are:

1. pH/blood gas instruments - measures blood pH, pCO_2 and pO_2 .
2. Co-oximeter instruments - measures total hemoglobin, oxyhemoglobin, carboxyhemoglobin and methemoglobin.
3. ISE Electrolyte instruments - measures electrolyte (such as sodium and, potassium) content of blood.

It is common practice to employ control solutions for verifying the accuracy and reliability of these instrumentation systems. A different control solution is used for each instrument. For example, a separate and distinct control solution is used to test the blood gas analyzer. A separate and distinct control solution is used to test the co-oximeter and a third separate and distinct solution is needed to test the ion analyzer. In other words, most pH/blood gas control materials serve as controls only for pH, pCO_2 and pO_2 . The blood gas controls that are formulated with hemoglobin solution or stabilized red blood cells do provide

-2-

control values for total hemoglobin in co-oximetry, but have no control values for either the other hemoglobin fractions or for electrolyte values.

Controls for hemoglobin fractions for use with
05 co-oximetry instrumentation systems do not provide parameters for use as controls with pH/blood gas analyzers or for ISE electrolyte analyzers. Similarly, controls for ISE instrumentation are not useable for either pH/blood gas or co-oximetry
10 instruments (in addition, some controls contain preservatives or other ingredients which make the material unsuitable for use in another type of instrument).

Summary of the Invention

15 This invention discloses a synthetic control solution which provides control parameters for three types of instrument systems: pH/blood gas, co-oximeters and ISE electrolytes instruments.

The synthetic liquid control is comprised of an
20 aqueous solution buffered to a pH of from about 7.1 to 7.7 and containing sufficient bicarbonate ion to provide a pCO_2 of from about 15 to about 80 after subsequently equilibrated with the desired levels of gaseous carbon dioxide, gaseous oxygen to provide a
25 pO_2 of from about 50 to 400, retained dyes to provide measurements of several hemoglobin fractions and salts of ions to provide measurements of these ions in solution.

Detailed Description of the Invention

This invention discloses a synthetic liquid control standard comprised of an aqueous solution buffered to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ion to provide a pCO₂ of from about 15 to about 80 after subsequently equilibrated with the desired levels of gaseous carbon dioxide, gaseous oxygen to provide a pO₂ of from about 50 to about 400 retained, dyes to provide measurements of total hemoglobin and of several hemoglobin fractions, sodium and potassium salts to provide measurements of these ions in solution.

In order to provide the desired pH for the respective normal, acidosis or alkalosis conditions, a buffer material should be selected which has a pK_a close to the desired working pH. A particularly useful buffer material for providing the desired pH conditions in the control solution of this invention is N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) which has a pK_a of 7.31 at 37°C. Other suitable buffer materials are, for example, N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (TES), which has a pK_a of 7.16 at 37°C.; 3-(N-morpholino) propanesulfonic acid (MOPS), which has a pK_a of 7.01 at 37°C.; and Tri-(Hydroxymethyl) aminomethane (TRIS) which has a pK_a of 7.77 at 37°C. These and other such suitable buffer materials, including the sodium salt derivatives, are described by Good et al. Biochemistry 5, 467-77 (1966) and Ferguson et al., Analytical Biochemistry 104,

-4-

300-310 (1980), the teachings of which are hereby incorporated by reference.

The desired pCO_2 level is provided in part by addition of bicarbonate ion, for example, $NaHCO_3$, to
05 the aqueous solution that a pCO_2 of from about 15 to about 80 is reached after subsequently equilibrated with the desired levels of gaseous carbon dioxide.
The desired pO_2 level of from about 50 to about 400 is facilitated by addition of gaseous oxygen to the
10 solution or the head space in the receptacle containing the aqueous solution. Addition of gaseous carbon dioxide similarly can facilitate maintenance of the aforesaid desired pCO_2 levels.

In a typical co-oximeter, a whole blood sample
15 is aspirated into the instrument, mixed with diluent, hemolyzed, and brought to a constant temperature in a cuvette. A microcomputer calculates the total hemoglobin concentration present, expressed in grams per one hundred milliliters of
20 whole blood g/dL THb. A typical co-oximeter also measures the percent oxyhemoglobin (O_2Hb), carboxyhemoglobin (COHb), methemoglobin (MetHb), and reduced hemoglobin. Each of these species of hemoglobin will absorb light at different wave-
25 lengths along the 500-650 nm range.

The control solution of the present invention contains absorbance means, such as dyes, which can absorb light in the 500-650 nm range at approximately the same percentage and wavelength as predetermined concentrations of the different hemoglobin

-5-

species. By using this control solution with the co-oximeter, it can be determined whether or not the co-oximeter is functioning properly and whether or not the instrument needs to be recalibrated.

05 The absorbance means need not absorb light exactly as the different species of hemoglobin do. What is important is that a relationship can be determined such that the light absorbed by the absorbance means in the control solution can be 10 correlated to a specific absorbance level of the particular hemoglobin species in question.

In a preferred embodiment, the control solution of the present invention contains a combination of Acid Red Dye #27 (CI 16185), Acid Yellow Dye #23 (CI 15 19140) and Acid Blue Dye #9 (CI 42090). Also used is the combination of Ponceau 3R Red Dye (CI 16155) and Acid Blue Dye (CI 42090).

The blue dye is used because it has a maximum absorbance of light at 630nm as does methemoglobin.

20 The red dyes were chosen due to the fact that they show absorbance levels at the 560nm and 535nm wavelengths as does oxyhemoglobin, at the 570nm wavelength as does carboxyhemoglobin, and at the 25 550nm wavelength as does reduced hemoglobin. By altering the concentrations of these dyes in the control solution, the control solution can simulate samples of blood having various levels of the different fractions of hemoglobin and of total hemoglobin.

Also contained within the control solution of this invention are predetermined amounts of electrolytes for testing ISE Electrolyte instruments. These electrolytes are placed into 05 solution with constant ionic strength by dissolving the approximate amount of the salts of these electrolytes. The electrolytes most often tested are sodium and potassium ions. Therefore, controls having a measurable range of electrolyte values of 10 Na and K can be made by the addition of appropriate quantities of sodium and potassium salts, such as NaCl and KCl.

In a preferred embodiment of this invention, the concentration of Na ions result from the 15 combination of the salts of the acid dyes as well as the addition of NaOH, NaCl, NaN₃ and NaHCO₃.

The density of the control solution can be placed at 1.01 to 1.03 and the viscosity of the solution from 2 to 4 centipoises which are similar 20 to the density and viscosity of blood by adding up to 70 g/L of natural polymers, such as bovine serum albumin, or one of the synthetic polymers such as Polyethylene glycol (PEG) 8000, Polyvinylpyrrolidone (PVP) 40, Polyvinyl alcohol (PVA) and Ficoll 400. 25 (Ficoll 400 is a synthetic high polymer made by the copolymerization of sucrose and epichlorohydrin produced by the Pharmacia Fine Chemicals AB Company of Uppsala, Sweden. Ficoll 400 indicates that the polymer has a molecular weight of approximately 30 400,000.)

-7-

To ensure a stable long shelf life of more than two years at room temperature, a chemical preservative such as sodium azide or formaldehyde can be added to the solution, or the solution can be
05 sterilized by either membrane filtration or by high temperature sterilization if the solution does not contain the polymers used to increase the viscosity of the solution.

Two preferred formulations are listed below.

- 10 By varying the concentrations of the reagents in the following formulations a varied number of control standards can be produced. These control standards will then have different levels of pH, pCO₂, PO₂, total hemoglobin fractions and concentrations of
15 sodium and potassium ions.

Formulation I

	Compound	Concentration
	HEPES and/or TRIS, MOPS	20 to 100 mM
	NaCl	40 to 100
20	KCl	2 to 8
	NaOH	0 to 60
	NaHCO ₃	18 to 26
	Acid Red Dye #27 (CI 16185)	2 to 5
	Acid Yellow Dye #23 (CI 19140)	3 to 7
25	Acid Blue Dye #9 (CI 42090)	0.015 to 0.08
	Polymer (PVA, Ficoll 400, PEG 8000, PVP 40 or Bovine serum albumin)	0 to 50 g/l

-8-

Formulation II

	Compound	Concentration
05	HEPES and/or TRIS, MOPS	20 to 100 mM
	NaCl	40 to 100
	KCl	2 to 8
	NaOH	0 to 60
	NaHCO ₃	18 to 26
	NaN ₃	0 to 40
10	Formaldehyde	0 to 60
	Ponceau 3R Red Dye (CI 16155)	5 to 11
	Acid Blue Dye #9 (CI 42090)	0.015 to 0.08
	Polymer (PVA, Ficoll 400, PEG 8000 or Bovine serum albumin)	30 to 70 g/l

15 Using varying amounts of the reagents from the preferred formulations, three levels of multiple control standards can be formulated, namely Level I Control, Level II Control and Level III Control.

20 The multiple control standard of Level II simulates normal blood having a pH of about 7.4, a pCO₂ of about 40mm Hg and pO₂ of about 100mm Hg. The multiple control standard of Level II contains a sufficient concentration of dye to simulate a total hemoglobin concentration of about 14g/100ml of 25 blood. This total hemoglobin reading can be produced by placing red dye, yellow dye and blue dye

-9-

into solution to give the control standard the ability to absorb the light spectrum in the wavelengths between 400 to 650nm. The yellow dye is used in order to give the control the appearance of blood but does not absorb light in the critical ranges. A preferred concentration of dyes is about 3.5mM of Acid Red Dye #27 (CI 16185), about 5mM of Acid Yellow Dye #23 (CI 19140) and about 0.04mM of Acid Blue Dye #9 (CI 42090). This concentration of dyes in solution results in a control standard having an appearance of blood and giving a total hemoglobin reading of about 14 grams in 100ml of aqueous solution as measured by the Corning 2500 Co-oximeter, 9g/100ml by the IL282 Co-oximeter and 26g/100ml by the ABL-30 Blood Gas Analyser. The multiple control standard of Level II also contains a concentration of sodium ions of about 140mM and a concentration of potassium ion of about 5mM.

The multiple control standard of Level I simulates blood having a low pH of 7.10 to 7.20, a high pCO_2 of from about 60 to 70mm Hg, and a low pO_2 of from about 50 to 65mm Hg. (This control standard thus simulates acidosis.) The control standard of Level I also contains a low concentration of Na ions from about 115 to 125mM and a low concentration of K ions from about 2.5 to 3.5mM.

The multiple control standard of Level I also contains a lower concentration of all dyes to simulate a total hemoglobin of about 9g/100ml of blood as read by the Corning 2500 Co-oximeter. A

-10-

preferred control solution of Level I contains about 2mM of Acid Red Dye #27 (CI 16185), about 3mM of Yellow Dye #23 (CI 19140), and about 0.015 mM of Acid Blue Dye #9 (CI 42090).

05 The multiple control standard of Level III simulates a sample of blood having a high pH of about 7.6, a low pCO₂ of about 22mm Hg and a high pO₂ level of about 150mm Hg. (This control standard thus simulates alkalosis). The multiple control
10 standard of Level III also contains a sufficient concentration of dye to simulate a high total hemoglobin of about 18g/100ml of solution. This total hemoglobin reading is produced by having a higher concentration of all dyes, preferably about
15 5mM of Acid Red Dye #27 (CI 16185), about 7mM of Acid Yellow Dye #23 (CI 19149), and about 0.08mM of Acid Blue Dye #9 (CI 42090). The control standard of Level III also contains a higher concentration of sodium ions 160mM and of potassium ions of about
20 7mM.

The desired pCO₂ value is provided in part by the addition of bicarbonate ion, e.g. NaHCO₃ to the aqueous solution. CO₂ gas is then added to the aqueous solution until a pCO₂ of from about 15 to
25 about 80mm Hg is attained, depending upon which control level is being produced.

The desired pO₂ level of from about 50 to 160mm Hg, depending upon which control level is being produced, is reached by the addition of gaseous
30 oxygen to the solution and head space in the

-11-

receptacle containing the aqueous solution. Addition of gaseous carbon dioxide similarly can facilitate maintenance of the aforesaid desired pCO₂ levels.

05 The final control standard solution is retained in a sealed or air-tight receptacle such as, for example, a glass vial or ampule to retain the desired gas equilibrium. The head space in the receptacle can be filled with an appropriate gas to 10 facilitate the provision of the aforesaid pCO₂ conditions. For example, for the acidosis blood gas control, a mixture of 65% oxygen, 5.9% of carbon dioxide and 87.6% of nitrogen is used. For the normal blood gas control a mixture of about 4.1% of 15 carbon dioxide, 11.8% of oxygen and 84.1% of nitrogen is used. For the alkalosis blood gas control a mixture of about 2.3% of carbon dioxide, 18% of oxygen and 79.7% of nitrogen is used. It will be appreciated that any other inert gas can be 20 used as a substitute for part or all of the nitrogen portion of the head space in the foregoing illustrative examples.

The following specific and detailed example will further illustrate the invention although it 25 will be appreciated that this example is not meant to restrict the invention to the specific details found in such example.

-12-

EXAMPLE

The blood gas control liquids are preferably formulated to represent three levels of pH, PCO₂ and PO₂ values to have different combinations of dye

05 concentration that simulate three levels of hemoglobin values and the visual appearance of hemolyzed blood plus three different levels of both sodium and potassium ions.

A preferred embodiment of the invention has the
10 following formulation:

	<u>COMPOUND</u>	<u>CONCENTRATION</u>
	HEPES	40 mM
	NaCl	40 to 100 mM
	KCl	2 to 8 mM
15	NaOH	20 to 30 mM
	NaHCO ₃	

Three different buffers were made using HEPES, NaOH, NaCl, KCl and NaHCO₃ in different concentrations. They were:

	<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
	HEPES 40.0 mM	40.0 mM	40.0 mM
	NaOH 20.0	25.7	29.6
	KCl 3.0	5.0	7.0
	NaCl 73.2	81.5	99.3
25	NaHCO ₃ 21.3	23.9	19.4

Three different levels of dyes were added to the corresponding buffer solutions.

	<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
	Red		
30	Dye #27 2.34 mM	3.72 mM	4.84 mM

-13-

Yellow

Dye #23	1.57	2.6	3.39
---------	------	-----	------

Blue

Dye #9	0.016	0.04	0.08
--------	-------	------	------

05 The buffered dye solutions were then separately placed in a container which was thermally controlled to 25°C. The appropriate gas mixture was then bubbled through each solution at a rate of 5 to 7 L/min. until the pH, PCO₂ and PO₂ reached equilibrium values, as determined by appropriate blood gas analyzers. The gas mixtures used had the following compositions:

	<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
	CO ₂	6.5%	4.1%
15	O ₂	5.9	11.8
	N ₂	87.6	84.1

After equilibrium was reached, the gaseous solution was subdivided into 2.6 ml quantities and placed into 3ml glass ampules which had been purged 20 with the same gas mixture used in bringing the solution to equilibrium. The filled ampules were heat-sealed.

The control liquid had an appearance of a hemoglobin solution and showed the corresponding 25 hemoglobin value equivalents as the following table:

-14-

	THb	O ₂ Hb%	O ₂ SAT%	COHb%	MethHb%	O ₂ Ct	Vol%O ₂
<u>ACIDOSIS (I)</u>							
Corning 2500	9.0g±0.5g/ 100 ml	-43±3	70±5	63±5	-5.3±0.3		
IL 282	5.5±0.5	-38±3	112±5	0.9±0.2	-2.9±0.3		
<u>Normal (II)</u>							
Corning 2500	14.±0.5	-40±3	65±5	64±5	-7.5±0.4		
IL 282	8.8±0.5	-35±3	101±5	6.9±0.5	-4.2±0.3		
<u>Alkalosis (III)</u>							
Corning 2500	18±0.5	-39±3	64±5	64±5	-9.4±0.4		
IL 282	11.5±0.5	-32±3	93±5	11.9±0.5	-5.0±0.3		

-15-

The formulated liquid also had three levels of concentration of sodium and potassium as measured by the following different models of ion selective electrode instrumentation:

		<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
05	Na			
	Corning 902	120±3mM	140±3mM	165±4mM
	614	120±3mM	140±3mM	165±4mM
	Nova - 1	120±3mM	140±3mM	160±4mM
10	IL-501	120±3mM	140±3mM	160±4mM
	K			
	Corning 902	3.0±0.3mM	5.0±0.3mM	7.4±0.4mM
	614	3.0±0.3mM	5.0±0.3mM	7.4±0.4mM
	Nova - 1	3.0±0.3mM	5.0±0.3mM	7.0±0.4mM
15	IL-501	3.0±0.3mM	5.0±0.3mM	7.0±0.4mM

The ampuled formulated liquid has the corresponding values of pH, PCO₂ and PO₂ for the blood gas analyzers.

		<u>Acidosis (I)</u>	<u>Normal (II)</u>	<u>Alkalosis (III)</u>
20	pH (unit)	7.15 (7.10-7.20)	7.4 (7.38-7.42)	7.6 (7.58-7.62)
	PCO ₂ mm Hg	70 (66-72)	40 (38-42)	22 (20-24)
	PO ₂ mm Hg	60 (58-67)	102 (100-104)	150 (145-155)

Those values were measured at 37°C.

The ampules containing formulated liquid can be
25 heat sterilized at 15' PSI for 30 minutes for long term shelf life.

-16-

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific 05 embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

For example, it will be understood by one having ordinary skill in the art that other dye 10 combinations can be used which can absorb light as hemoglobin does. This invention is not limited to the illustrated examples of dye combinations.

Claims

1. A multiple liquid control standard for use in the quality assurance of blood analysis instrumentation systems, said liquid control standard being able to act as a control standard for blood gas instrumentation systems measuring pH, pCO₂ and pO₂ of blood, as a control standard for a co-oximeter measuring the amount of total hemoglobin present in the blood and the relative amounts of other hemoglobin fractions present in the blood, and as a control standard for ion selective electrode instrumentation systems measuring the concentration of electrolytes in the blood.
- 15 2. A multiple liquid control standard as recited in Claim 1, wherein the control standard is an aqueous solution buffered by a buffering agent to a pH of from about 7.1 to about 7.7 and containing sufficient bicarbonate ions to provide a pCO₂ from about 15 to about 80mm Hg, gaseous oxygen to provide a pO₂ of from about 50 to about 40.0mm Hg retained, absorbance means to provide a control test which corresponds to a predetermined level of hemoglobin and hemoglobin fractions, and salts of electrolytes to provide a control test for a corresponding ion selective electrode system.

3. A multiple liquid control standard as recited in Claim 2, wherein the buffering agent is selected from the group consisting of N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid, 3-(N-morpholino) propane sulfonic acid and tri-(hydroxymethyl) amino methane.
4. A multiple liquid control standard as recited in Claim 2, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185), and Acid Blue Dye #9 (CI 42090).
5. A multiple liquid control standard as recited in Claim 2, wherein the absorbance means is comprised of Ponceau 3R Red Dye (CI 16155) and Acid Blue Dye #9 (CI 42090).
- 15 6. The liquid control standard as recited in Claim 2, wherein said liquid control standard contains a predetermined concentration of Na and K ions so that the control standard can be used to test an ion selective electrode instrumentation system which measures the amount of Na and K ions present in blood.
- 20 7. A multiple liquid control standard as recited in Claim 2, wherein the density of said control standard is about from 1.01 to 1.03 and the viscosity of said control standard is about from 2 to 4 centipoises.

-19-

8. A multiple liquid control standard as recited in Claim 7, wherein the density and the viscosity of said control standard are adjusted by a polymer selected from the group consisting of Bovine serum albumin, Polyethylene glycol 8000, Ficoll 400, Polyvinylpyrrolidone 40, and Polyvinyl alcohol.
9. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about 7.10 to 7.20, the pCO₂ ranges from about 60 to 70mm Hg, the pO₂ ranges from about 50 to about 65mm Hg, the Na ion concentration ranges from about 115 to about 125 mM, the K ion concentration ranges from about 2.5 to about 3.5 mM and the absorbance means simulates blood having a low level of total hemoglobin.
10. A multiple liquid control standard as recited in Claim 9, wherein the absorbance means is comprised of Acid Red Dye #27 (CI 16185) and Acid Blue Dye #9 (CI 42090).
11. A multiple liquid control standard as recited in Claim 9, wherein the absorbance means is comprised of Ponceau Red Dye 3R (CI 16155) and Acid Blue Dye #9 (CI 42090).
12. A multiple liquid control standard as recited in Claim 2, wherein the pH ranges from about

-20-

- 7.35 to 7.45, the pCO_2 ranges from about 35 to
45mm Hg, the pO_2 ranges from about 95 to about
110mm Hg, the Na ion concentration ranges from
about 135 to about 145 mM, the K ion concen-
05 tration ranges from about 4.5 to about 5.5 mM
and the absorbance means simulates blood having
a normal level of total hemoglobin.
13. A multiple liquid control standard as recited
in Claim 12, wherein the absorbance means is
10 comprised of Acid Red Dye #27 (CI 16185) and
Acid Blue Dye #9 (CI 42090).
14. A multiple liquid control standard as recited
in Claim 12, wherein the absorbance means is
15 comprised of Ponceau Red Dye 3R (CI 16155) and
Acid Blue Dye #9 (CI 42090).
15. A multiple liquid control standard as recited
in Claim 2, wherein the pH ranges from about
7.55 to 7.65, the pCO_2 ranges from about 15 to
25mm Hg, the pO_2 ranges from about 140 to about
20 160mm Hg, the Na ion concentration ranges from
about 150 to about 170 mM, the K ion concen-
tration ranges from about 6.5 to about 7.5 mM
and the absorbance means simulates blood having
a high level of total hemoglobin.
- 25 16. A multiple liquid control standard as recited
in Claim 15, wherein the absorbance means is

comprised of Acid Red Dye #27 (CI 16185) and
Acid Blue Dye #9 (CI 42090).

17. A multiple liquid control standard as recited
in Claim 15, wherein the absorbance means is
comprised of Ponceau Red Dye 3R (CI 16155) and
Acid Blue Dye #9 (CI 42090).

18. A multiple control standard for use in the
quality assurance of blood analysis
instrumentation systems, said liquid control
standard being able to act as a control
standard for blood gas instrumentation systems
measuring pH, pCO₂ and pO₂ of blood, as a
control standard for a co-oximeter measuring
the amount of total hemoglobin present in the
blood and the relative amounts of other
hemoglobin fractions present in the blood, and
a control standard for ion selective electrode
instrumentation systems measuring the
concentration of Na and K ions in the blood,
wherein the control standard is an aqueous
solution buffered by a buffering agent to a pH
of from about 7.1 to about 7.7 and containing
sufficient bicarbonate ion to provide a pCO₂
from about 15 to about 80mm Hg, gaseous oxygen
to provide a pO₂ of from about 50 to about
400mm Hg retained, absorbance means to provide
a control test which corresponds to a
predetermined level of hemoglobin and

hemoglobin fractions, said absorbance means
being comprised of Acid Red Dye #27 (CI 16185)
and Acid Blue Dye #9 (CI 42090), and salts of
Na and K to provide a control test for a
05 corresponding ion selective electrode instru-
mentation system.

19. A multiple control standard for use in the
quality assurance of blood analysis instru-
mentation systems, said liquid control standard
10 being able to act as a control standard for
blood gas instrumentation systems measuring pH,
 pCO_2 and pO_2 of blood, as a control standard
for a co-oximeter measuring the amount of total
hemoglobin present in the blood and the rela-
15 tive amounts of other hemoglobin fractions
present in the blood, and a control standard
for ion selective electrode instrumentation
systems measuring the concentration of Na and K
ions in the blood, wherein the control standard
20 is an aqueous solution buffered by a buffering
agent to a pH of from about 7.1 to about 7.7
and containing sufficient bicarbonate ion to
provide a pCO_2 from about 15 to about 80mm Hg,
gaseous oxygen to provide a pO_2 of from about
25 50 to about 400mm Hg retained, absorbance means
to provide a control test which corresponds to
a predetermined level of hemoglobin and hemo-
globin fractions, said absorbance means being
comprised of Ponceau 3R Red Dye (CI 16155) and
30 Acid Blue Dye #9 (CI 42090).

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US87/00796

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³
According to International Patent Classification (IPC) or to both National Classification and IPC

IPC: GOIN/3100 ; US: 436/11

II. FIELDS SEARCHED

Minimum Documentation Searched ⁴

Classification System	Classification Symbols
US	436/11-18
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁶	

III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴

Category ⁸	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
A	US,A, 4,485,174, Published 27 Nov. 1984, (Chiang et al.)	1-19
A	US,A, 4,469,792, Published 04 Sept. 1984, (Simmonds et al.)	1-19
A	US,A, 4,458,021, Published 03 July 1984, (Herring.)	1-19
A	US,A, 4,163,734, Published 07 Aug. 1979, (Sorensen et al.)	1-19
Y	US,A, 4,279,775, Published 21 July 1981, (Louderback et al.).	1-19
Y	US,A, 4,369,127, Published 18 Jan. 1983, (Cormier et al.)..	1-19

* Special categories of cited documents: ¹⁵

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search ³

26 June 1987

Date of Mailing of this International Search Report ³

10 JUL 1987

International Searching Authority ¹

ISA/US

Signature of Authorized Officer ²⁰

T. J. Wallen

T. J. Wallen